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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/840,861	04/25/2001	Daniel Dupret	58763.000013	4902

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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 08/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/840,861	DUPRET ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,50-80 and 82-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,50-80 and 82-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action responds the Amendment received on May 28, 2004.

Preliminary Remark

In careful reconsideration of the application and the study of the prior art, the instant non-final rejection is necessitated.

All objections/rejections hereto not reiterated should be considered to be withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 69 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 69 is indefinite for the reciting the phrase, "polynucleotide bank comprises artificial polynucleotide sequences," because it is unclear what is implied by the term, "artificial." For example, it is unclear when a polynucleotide is considered artificial – synthesized, non-naturally occurring, processed, etc. Since the specification lacks both a specific and exemplary definition for said term, for the purpose of prosecution, said term is assumed to mean "processed."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 50-69, 70-73, 79, 80, 82, 83, 85-87, and 92 are rejected under 35 U.S.C. 102(e) as being anticipated by Pachuk et al. (U.S. Patent No. 6,143,527, issued November 7, 2000, filed May 6, 1997, priority May 6, 1996).

Pachuk et al. disclose an *in vitro* method employing a thermostable ligase, said method comprising the steps of:

i) providing oligonucleotide fragments comprising two heterologous polynucleotide sequences;

ii) hybridizing the fragments to a "bridging" oligonucleotide (or assembly matrix), said fragments oriented for ligation;

iii) ligating the hybridized fragments having immediately adjacent ends with a ligase to form a recombinant polynucleotide sequence; and

iv) selecting the recomobinant polynucleotide sequence that exhibits advantageous characteristics compared to corresponding characteristics of one or more reference sequence (Figures 1A, 10A and 10B, columns 3, lines 23-38), rendering claims 1 and 92 anticipated.

The term, "heterologous," is defined in the instant specification as, "two sequences whose base composition differs by at least one base." [0073]. As the method of Pachuk et al. employs two nucleic acids of at least a single different base, rendering this limitation anticipated.

Figure 1A evidences at least one repetition of providing, hybridizing or the ligating step, anticipating instant claims 50 and 55.

The ligase-mediated method of Pachuk et al. is disclosed as producing a chimeric kanamycin resistant gene via ligation of different sequences (column 3, lines 23-28; column column 20, lines 50-67; column 20, lines 24-45), rendering the limitation of "selecting the recombinant polynucleotide sequence that exhibits advantageous characteristics" and instant claims 51 and 52 anticipated.

Pachuk et al. employ a polymerase in filling in the gaps between the two heterologous nucleic acids, followed by the their ligation (Figure 9A through 9C), rendering instant claim 53 anticipated.

Pachuk et al. disclose an embodiment of the method, wherein the two heterologous nucleic acids are located immediately adjacent to each other, hence not needing a polymerase to fill-in the gaps therebetween (Figure 1A), thereby anticipating instant claim 54.

Pachuk et al. disclose that the two heterologous are generated by various methods such as restriction enzyme digestion fragment, DNAse digestion, chemical cleavage, enzymatic or chemical synthesis (Abstract) and that the advantage of employing the "bridging oligonucleotide" (or an assembly matrix) is in its, "ability to ***site-specifically ligate*** two or more DNA mmolecules containing compatible or non-compatible termini," (column 6, lines 31-34;

column 14, line 59 through column 15, line 2), thereby anticipating instant claims 56-61, 69, 71, 75, and 79).

Figure 10A and 10B disclose that the method is employed to generated chimeric kanamycin resistance gene by ***recombination of gene*** sequence from pUC4K, the ***coding region*** from ant(4')-Ia ***gene*** in pUB110 to ***generate a recombinant gene*** disclosed by Figure 10B followed by cloning (column 15, lines 13-15), rendering instant claims 62-65, 71-73, and 87 anticipated. The nucleotide fragments employed in this embodiment comprise selection of polynucleotides offering advantageous characteristics as the above sections are ligated to form a kanamycin resistance gene. As the instant specification defines "restricted bank" as bank having polynucleotides which are selected as having advantageous characteristics, the polynucleotide fragments employed in the method of Pachuk et al. would anticipate the limitation of instant claim 71. The method would necessarily require that the formed recombinant polynucleotide sequence be separated from the bridging oligonucleotides, rendering instant claim 83 anticipated.

The embodiment of the two double stranded heterologous nucleic acids first being denatured prior to the ligation-mediated assembly is also disclosed by Pachuk et al. (column 8, lines 56-59), rendering instant claims 66, 67, and 80 anticipated.

Pachuk et al. disclose that following the hybridization of the nucleic acid fragments to the bridging oligonucleotides, at temperatures 68-72°C, ligation is performed, rendering instant claim 68 anticipated. Additional evidence that the termostable-ligase employed by Pachuk et al. is functional at temperatures at least 65°C is evidenced by the product description of the T4 ligase employed by Pachuk et al., the description of which is attached hereto (also available through www.epicentre.com).

With regard to the use of the recombinant polynucleotide sequence as a source of assembly matrix during at least one repetition as recited in instant claims 82 and 86, Figure 1A, the nucleic acid "5s" and column 5, lines 20-26 clearly anticipates such limitation. The use of combination of bridging oligonucleotide with the use of recombined nucleic acid "5s" would necessarily anticipate instant claim 70.

Pachuk et al. further disclose that the recombinant product is amplified via PCR for cloning (column 15, lines 11-15), rendering instant claim 85 anticipated.

Therefore, Pachuk et al. anticipate the invention as claimed.

Claims 1 and 88-91 are rejected under 35 U.S.C. 102(a) as being anticipated by Coco et al. (Nature Biotechnology, April 2001, vol. 19, pages 354-359).

The instant rejection predicated on the fact that the parent application 09/723,316, does not have a proper written support under 35 U.S.C. 112, first paragraph, for the limitation of cleaving the single strand overlaps with endonuclease such as Flap endonuclease. The effective filing date for the instant claims, therefore, has been determined to be April 25, 2001.

Coco et al. disclose a method of producing recombinant polynucleotide, said method comprising the steps: i) of providing a pool of nucleic acid fragments; ii) hybridizing the fragments to an assembly matrix so that the hybridized fragments are oriented for ligation; iii) ligating the fragments; and selecting the recombinant polynucleotide sequence (Figure 1).

Coco et al. disclose that the possible single-strand overlaps of non-hybridized ends could be cleaved by the use of nuclease (Figure 1), wherein the enzyme is Taq polymerase which comprise flap endonuclease activity (page 358, 2nd column).

Therefore, the invention as claimed is anticipated by Coco et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 74-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pachuk et al. (U.S. Patent No. 6,143,527, issued November 7, 2000, filed May 6, 1997, priority May 6, 1996) in view of Stemmer et al. (U.S. Patent No. 6,117,679, issued November 12, 2000, filed March 25, 1996, priority February 17, 1994).

The teachings of Pachuk et al. have been discussed above.

Pachuk et al. do not explicitly disclose that the fragment could be served as an assembly matrix (instant claims 74).

Pachuk et al. do not explicitly disclose various methods of providing the nucleic acid fragments involved in the ligation mediate method (instant claims 75-78).

Stemmer et al. disclose a method of generating recombinant polynucleotide via overlapping amplification reaction, wherein nucleic acid fragments are generated via random fragmention or via treatment with DNAse I (column 23, lines 24-29), meeting the limitations of claims 75-78.

Stemmer et al. employ the method of employing overlapping nucleic acid fragments in generating recombined polynucleotides, said method comprising the steps of hybridizing

fragments of nucleic acids to another fragment of nucleic acid to conduct recombination (instant claim 74.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to expand the teachings of Pachuk et al. with the teachings of Stemmer et al. to arrive at the claimed invention for the following reasons.

The motivation to expand the teaching of Pachuk et al. is provided by the artisans wherein said artisans employ a bridging oligonucleotide to site-specifically join two ends of oligonucleotides, wherein said ligated oligonucleotides produce selectively advantageous characteristics (column 6, lines 31-34; column 14, line 59 through column 15, line 2; and column 15, lines 13-15).

Stemmer et al. disclose a method of recombining a plurality of nucleic acid sequences derived from different heterologous sequence banks for generating recombinant polynucleotide sequences displaying advantageous characteristics, wherein a pool of polynucleotide sequences are employed. Stemmer et al. is explicit in stating that in practicing the recombination or shuffling method, such method could involve not only PCR amplification, or similar amplification method, ***but also*** site-specific recombination, chimera formation (column 24, lines 53-65).

Having provided with such disclosure, one of ordinary skill in the art at the time the invention was made would have been motivated to expand the site-specific recombination method of Pachuk et al. with the teachings of Stemmer et al. in order to generate a recombined polynucleotide exhibiting selective characteristics.

One of ordinary skill in the art would have had a clear expectation of success at combining the teachings because the teachings of the both artisans generated a recombinant polynucleotide sequence exhibiting an advantageous characteristic that is not naturally occurring, in view of the explicit statement of Stemmer et al. in that any method, such as site-specific recombination method, could be employed in their method of nucleic acid shuffling method.

Therefore the invention as claimed is *prima facie* obvious over the cited references.

Claims 84 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pachuk et al. (U.S. Patent No. 6,143,527, issued November 7, 2000, filed May 6, 1997, priority May 6, 1996) in view of Dolganov (U.S. Patent No. 5,821,091, issued October 13, 1998, filed January 26, 1996).

The teachings of Pachuk et al. have been discussed above.

While Pachuk et al. isolate the chimeric polynucleotide sequence produced, artisans are not explicit in what method was employed the isolation step (instant claim 84).

Dolganov discloses a well-known method of incorporating biotinylated nucleotides for subsequent isolation of amplified (or desired) nucleic acid sequences (column 28, lines 36-60).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ a well-known marker-assisted labeling technique, as evidenced by Dolganov, in order to first isolate the recombinant polynucleotide sequence produced by the method of Pachuk et al. so that by doing so, said recombinant polynucleotide sequence would be available for the subsequent cloning of Pachuk et al. As one of ordinary skill in the art would have recognized for the recombinant polynucleotide to be cloned and expressed, isolation of the

polynucleotide would have been necessary. Therefore, one of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success at employing any of the well-known polynucleotide isolation techniques for the subsequent cloning reaction.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Claims 88-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pachuk et al. (U.S. Patent No. 6,143,527, issued November 7, 2000, filed May 6, 1997, priority May 6, 1996) in view of Coco et al. (Nature Biotechnology, April 2001, vol. 19, pages 354-359)

The instant rejection predicated on the fact that the parent application 09/723,316, does not have a proper written support under 35 U.S.C. 112, first paragraph, for the limitation of cleaving the single strand overlaps with endonuclease such as Flap endonuclease. The effective filing date for the instant claims, therefore, has been determined to be April 25, 2001. Further, the present 103(a) rejection relies on the digestion of non-hybridizing flaps of Coco et al. and should not in anyway, be confused with the 102(a) rejection made above.

The teachings of Pachuk et al. have been discussed above.

Pachuk et al. do not explicitly disclose that non-hybridized overlapping ends of the nucleic acid fragments be cleaved by nuclease, specifically Flap endonuclease (instant claims 88-91).

Coco et al. disclose a method of producing recombinant polynucleotide, said method comprising the steps: i) of providing a pool of nucleic acid fragments; ii) hybridizing the fragments to an assembly matrix so that the hybridized fragments are oriented for ligation; iii) ligating the fragments; and selecting the recombinant polynucleotide sequence (Figure 1).

Coco et al. disclose that the possible single-strand overlaps of non-hybridized ends could be cleaved by the use of nuclease (Figure 1), wherein the enzyme is Taq polymerase which comprise flap endonuclease activity (page 358, 2nd column).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modifying the teachings of Pachuk et al. to cleave the "possible" non-hybridized ends of the nucleic acid fragments generated via use of an enzyme well-known to cleave a single stranded nucleic acid, such as Flap endonuclease, as evidenced by Coco et al.

Coco et al. clearly disclose the possibility of producing non-overlapping single-stranded nucleic acid fragments when hybridized to a bridging oligonucleotide (or "bottom strand scaffold", Figure 1, Coco et al.). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to remove the non-overlapping single-stranded nucleic acid fragments via use of well-known endonucleases such as Flap endonuclease to arrive at the claimed invention with a reasonable expectation of success.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

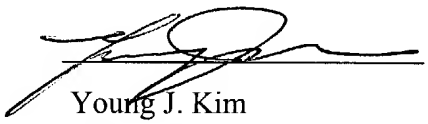
Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner can normally be reached from 8:30 a.m. to 6:00 p.m. Monday through Thursday. If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (571) 272-0784. If the attempts to

reach the above Examiners are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782. Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (703) 872-9306. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.



Young J. Kim
Patent Examiner
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YOUNG J. KIM
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yjk